Br. J. clin. Pharmac. (1985), **20**, 238–240

The effects of sucralfate upon phenytoin absorption in man

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The possible influence of sucralfate on phenytoin absorption was investigated in a double-blind, placebo controlled study. Concomitant administration of 1 g sucralfate reduced the absorption of 300 mg phenytoin capsules by 20% as measured by the area under the curve from 0–48 h. This could be of significance in epileptic patients stabilised on phenytoin in whom sucralfate is used in ulcer treatment.

Keywords sucralfate phenytoin interaction

Introduction

Sucralfate (Antepsin, Ayerst Laboratories Ltd) is a complex aluminium hydroxide salt of a sulphated disaccharide used in the treatment of peptic ulceration. It probably binds with proteins in the ulcer base to form a chemical barrier to further erosion.

However, if sucralfate possessed more general binding properties it could inhibit the absorption of other drugs taken concomitantly. We have therefore examined the effect of sucralfate administration upon phenytoin absorption.

Methods

Eight healthy male volunteers (age range 21–28 years) participated in a double-blind placebo controlled cross-over study approved by the University of Nottingham Medical School Ethical Committee. After an overnight fast they took phenytoin 300 mg (3 × 100 mg Epanutin capsules; Parke Davis & Co.) together with sucralfate (Antepsin) 1 g or an identical placebo with 200 ml of water. Fasting continued for a further 4 h but normal everyday activities were allowed, except that the subjects were encouraged to avoid ethanol for 1 week before and for the duration of the study. Blood (10 ml) for phenytoin assay was taken immediately prior to drug ingestion and at 2, 4, 6, 8, 10, 12, 24 and 48 h afterwards. The serum was frozen prior to assay.

Phenytoin assay

Serum phenytoin was assayed by high performance liquid chromatography.

Phenytoin and methyl-phenyl-phenylhydantoin stock solutions 1 mg ml^{-1} were prepared in methanol. Subsequent dilutions were made with distilled water. All solvents were chromatographic grade: potassium phosphate was Analar grade.

Serum (1 ml) was mixed for 10 s with 2 ml 0.1 M phosphate buffer pH 5.0 and 100 μl of the internal standard (5-[*p*-methylphenyl]5-phenylhydantoin 20 μg ml^{-1}) added. Dichloromethane (5 ml) was added and mixed on a rotary shaker for 10 min. Samples were centrifuged at 2000 rev min^{-1} for 10 min and the resulting upper aqueous layer aspirated under vacuum. The remaining organic layer was transferred to a conical tube and evaporated to dryness under air at 50°C. The dried residue was reconstituted in 50 μl of mobile phase and vortexed for 20 s. 100 μl were injected for analysis.

Chromatographic conditions Samples were injected into a spherisorb 5 μ O.D.S. column (25 cm × 46 mm i.d.) using a 100 μl loop Rheodyne 7010 injector coupled to a Magnus M7110 Autosampler. With the L.D.C. uv Monitor III Detector set at 0.008 AUFS, chromatograms were recorded and integration performed by a Waters 730 Data Module. The mobile phase was 0.01 M KH_2PO_4: methanol/

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acetonitrile 40/10 (65 : 35) adjusted to a final pH of 3.5 with 1 M H_3PO_4 before passage through an 0.4 μ filter under vacuum and degassing for 10 min. The mobile phase flow rate was 1.5 ml min^{-1} using a Waters 6000A pump and the analytes were measured at an absorption wavelength of 254 nm.

Analytical results Calibration curves were produced for phenytoin ranging in concentration from 500 ng ml^{-1} – 10 μg ml^{-1}, by plotting the peak height ratios of phenytoin to the internal standard against the respective phenytoin concentration. The relationship was linear over the calibration range given. (The linear regression correlation coefficient was 0.9968.) Recoveries of phenytoin from serum varied from 82% to 100% for the concentrations of 0.5 μg ml^{-1} and 5 μg ml^{-1} respectively. Inter-assay variability ranged from 5.1% for 0.5 μg ml^{-1} to 3% for 5 μg ml^{-1} samples. Intra-assay variability was 3%. The limit of sensitivity for the phenytoin assay was 100 ng ml^{-1}.

Phenytoin absorption was assessed from the area under the curve to 48 h using the trapezoidal rule. We have assumed the elimination occurred with first order kinetics from the relatively low serum phenytoin concentrations achieved in this study. Statistical analysis was performed using a paired Student's *t*-test. The results are given as mean ± s.e. mean.

Results

The concomitant administration of sucralfate reduced phenytoin bioavailability as measured by AUC_{0-48} by 20% (Figure 1). This reduction was highly significant (AUC_{0-48} sucralfate 99 ± 10 μg ml^{-1} h, placebo 124 ± 11 μg ml^{-1} h, $t = 3.5$, $P < 0.005$).

Peak phenytoin levels also tended to be reduced with concomitant sucralfate treatment, although the change was not statistically significant (sucralfate 2.9 ± 0.4 μg ml^{-1}, placebo 3.7 ± 0.5 μg ml^{-1}, $t = 1.3$, $0.1 < P < 0.5$). The time to reach peak phenytoin levels was not formally analysed, being dependent upon the frequency of blood sampling, and was rendered difficult by the unusual shape of the phenytoin (sucralfate) curve.

Discussion

This double-blind placebo controlled cross-over study has shown that phenytoin absorption is significantly reduced when phenytoin and sucralfate are taken together. A similar, but slightly greater fall in phenytoin absorption was found in dogs by Lacz *et al.* (1982) who also demonstrated that the absorption was unaltered when phenytoin was given 2 h after sucralfate. They also examined digoxin, propranolol, quinidine and aminophylline absorption but found no changes.

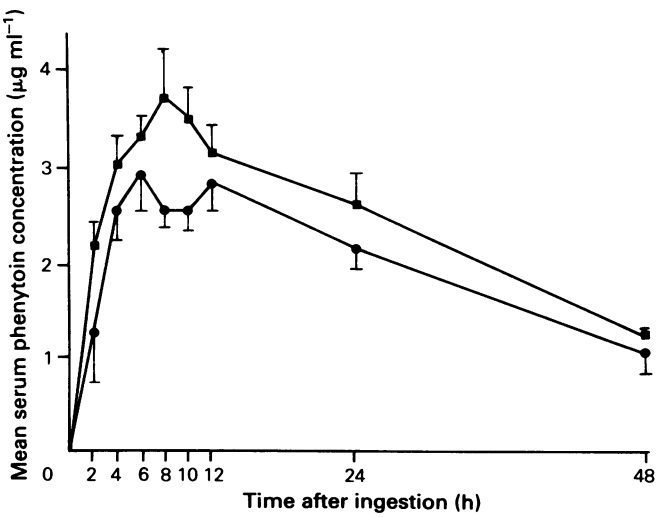

Figure 1 Mean serum phenytoin concentrations following concomitant ingestion of the drug with either sucralfate (●) or placebo (■) (mean ± s.e. mean).

In man interactions of sucralfate with warfarin (Mungall *et al.*, 1983) and cimetidine (Ritschell *et al.*, 1984) have been described which have been attributed to the interference of sucralfate with the absorption of these drugs. By contrast, Kamali *et al.* (1985) have found no interaction between sucralfate and paracetamol.

We can identify no factor which would predict whether the absorption of another drug is likely to be reduced by concomitant sucralfate ingestion. However, the 20% reduction in phenytoin absorption which we have observed with concomitant sucralfate administration could be enough to reduce steady state blood levels and seizure control could be lost as a result.

Antepsin and identical placebo were supplied by Ayerst Laboratories Ltd.

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(Received 10 April 1985, accepted 15 May 1985)